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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)	
119742-005	

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on _____

Signature _____

Typed or printed name _____

Application Number	Filed
10/681,788	October 8, 2003
First Named Inventor	
Habib Zaghouani, et al.	
Art Unit	**Examiner**
1644	Gerald R. Ewoldt

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 51,696
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

David B. Fournier
Typed or printed name

312.781.7167
Telephone number

October 30, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Habib Zaghouani
Appl. No.:	10/681,788
Conf. No.:	6701
Filed:	October 8, 2003
Title:	SUSTAINED TREATMENT OF TYPE 1 DIABETES AFTER EXPRESSION OF PREDISPOSITION MARKERS
Art Unit:	1644
Examiner:	Edwoldt, G.R.
Docket No.:	0119742-005

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

This paper is submitted in response to the final Office Action dated October 8, 2008.

I. Rejection under 35 U.S.C. § 112, first paragraph.

Claims 1-5, 7, 13, 15-19 and 22-30 stand rejected under 35 U.S.C. § 112, first paragraph on the alleged basis that there is "insufficient evidence that the claimed method could effectively function as a method for preventing or delaying the onset of type 1 diabetes (IDDM)." Office Action ("OA") dated 10/08/2008 at p. 3. This rejection omits one or more essential elements needed for a *prima facie* rejection; additionally, clear factual errors exist.

As a preliminary matter, it has been unclear during prosecution whether the instant § 112, first paragraph rejection is on the basis that the asserted utility is not credible (MPEP 2107.01IV), or under the "how to use" requirement of that paragraph. If the rejection is indeed based on an alleged lack of credible utility under §112, Applicants have previously established clear error as well as omission of essential elements required for such a *prima facie* rejection. See OA Response dated August 7, 2008, Section II (Page 9 – 15).

If the instant rejection, instead, relates to the "how to use" requirement of §112, first paragraph, clear factual errors as well as omissions in the *prima facie* rejection exist as are discussed below.

A. Omission of essential element needed for *prima facie* rejection.

It is settled law that a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enablement requirement of the first paragraph of § 112 ***unless*** there is reason to doubt the objective truth of the statements contained therein. MPEP 2164.04 citing *In re Marzocchi*, 58

C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971). Thus, the PTO has the initial burden of challenging a ***presumptively correct*** assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would ***reasonably doubt*** the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy*, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (CCPA 1981).

The PTO has simply not provided any evidence showing that one of ordinary skill in the art would ***reasonably doubt*** the asserted utility of the claimed invention and has therefore not met its initial burden. The only evidence provided by the PTO for lack of enablement shows that, using ***fundamentally different*** therapeutic agents than those claimed, tested in diseases ***other than*** Type 1 diabetes ("TID") as presently claimed, some researches have achieved tolerance results in animal models that have been difficult to reproduce in humans. See OA dated 10/08/2008 at page 3. Specifically, *Marketletter* deals with two unsubstituted peptides (much different than the claimed Ig-GAD2 fusion protein) tested in Multiple Sclerosis and Rheumatoid Arthritis, not TID. *Anderton* is a review article generally discussing administration of native antigen and analogue peptides in a Multiple Sclerosis model which, again, is a much different therapeutic modality than the claimed fusion protein and a different disease state than TID. Finally, *Dong* is merely a general review of tissue graft transplant tolerance (not to treatment of any autoimmune disorder let alone TID) and contains nothing to call in to question use of the ***presently claimed*** fusion protein construct for delaying or preventing TID. At most, these references are only tangentially related to the presently claimed invention in that they relate in various ways to tolerance. However, they simply do not cast any doubt, let alone any reasonable doubt, on the use of the ***presently clamed invention*** which entails an altogether different therapeutic agent and different disease state than those discussed in the cited references. Applicants respectfully submit that the burden of challenging the presumptively correct assertion of the manner of using the invention has not been met. Withdrawal of this rejection is therefore respectfully requested.

B. Clear Legal Error.

1. Post-filing date evidence *must* be considered and *can* be used to demonstrate enablement at the time of filing.

To further demonstrate that Applicants' claimed invention was enabled at the time of filing, Applicants submitted a declaration under 37 CFR 1.312 showing that the claimed method prevents and/or delays the onset of TID in the gold standard NOD mouse model for that disease. See Declaration of Dr. Habib Zaghouani ("Zaghouani Declaration") made of record December 19, 2007. The OA states that "the work [summarized in the Declaration] was apparently done after the effective filing date and therefore **cannot be relied upon to show enablement at the time of**

filing as is required." OA dated 10/8/2008, page 4, last paragraph – page 5, first paragraph (emphasis added). This statement is clearly erroneous. Contrary to the Examiner's position, both the MPEP and Federal Circuit case law are clear that post-filing date declarations can be used to demonstrate that the claimed invention was enabled when filed and **must be considered** when submitted. MPEP 2164.05 and *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

The *Brana* case is particularly on point. In *Brana*, the Federal Circuit stated in the context of a 112, first paragraph enablement rejection that "[e]ven if one skilled in the art would have reasonably questioned the asserted utility, *i.e.*, even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility." *Id* at 1567. In *Brana*, the applicants provided a post-filing date declaration showing that compounds within the scope of the claims exhibited significant anti-tumor activity against the L1210 standard tumor model *in vivo*. According to the court, such evidence alone should have been sufficient to satisfy applicants' burden. The court noted that "[t]he Kluge declaration, though dated ***after*** applicant's filing date, could be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. It does not render an insufficient disclosure enabling, **but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)**." (Emphasis added, internal citation omitted).

Like the declaration submitted in *Brana*, the Zaghouani Declaration submitted in the instant case also pertains to the accuracy of statements already in the specification and evidences that the original disclosure was in fact enabling when filed. Specifically, the Zaghouani Declaration illustrates the accuracy of disclosure in the specification (e.g. pages 45-46 and elsewhere) that the claimed Ig-GAD2 construct is useful for preventing and/or delaying onset of TID.

It was clear legal error for the Examiner to disregard the Zaghouani Declaration and to take the position that post-filing data submitted via declaration cannot be relied on to show enablement at the time of filing of the application. Withdrawal of this rejection is respectfully requested.

2. No requirement for human data exists.

The Examiner further takes the position that "while the invention might delay onset of diabetes in some experimental mice…it is not enabled for the prevention of disease in any species nor the preventing or delay of disease ***in humans***." OA dated 10/08/2008 at page 4 and 6. The Examiner attempts to support this conclusion by citing to instances in which treatment (albeit with a fundamentally different type of therapeutic agent and in different diseases than TID as discussed above) succeeded in animals but failed in humans—for example *Marketletter*. That position—the same position taken by the PTO and summarily rejected by the Federal Circuit in *Brana*—is also clear legal error.

In *Brana*, the PTO argued in the context of a 112, first paragraph rejection that *in vivo* test results in animals are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. *Id* at 20. In response, the Federal Circuit stated:

> The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption... proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel*, 48 C.C.P.A. 1116, 292 F.2d 948, 953...In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated: We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property **in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans**. *Id.* At 22. (emphasis added)

As has been clearly established in the record, the NOD mouse model used in the experiment described in the Zaghouani Declaration is considered the gold standard animal model for TID. See OA Response dated 08/07/2008, pages 12 – 13. It was clear error to reject the instant claims under 35 U.S.C. § 112, first paragraph on the alleged basis that successful results in the gold standard animal model for TID do **not** necessarily translate to humans. Withdrawal of this rejection is respectfully requested.

II. Rejection Under 35 U.S.C. 103(a).

Claims 1, 2, 4, 5, 7, 13, 15-19, 22-24 and 28-30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/30706 in view of Kaufman et al., J. Clin. Invest. Vol. 89 pp. 283-292 (1992) ("Kaufman"). Applicants respectfully submit that clear factual errors exist in this rejection and essential elements are missing from the *prima facie* case.

A. Clear Factual Errors.

The Examiner states that "[a]ll other claims [besides claim 26], however, encompass the use of **full length GAD65** which is obvious." OA at p. 7, 2nd paragraph (emphasis added). This statement is factually incorrect. Claim 1 as amended in the OA response dated 08/07/2008 (page 5) specifies that "the protein fragment or peptide **is GAD2 represented by SEQ. ID NO 4.**" (emphasis added). As is disclosed at page 45 of the instant specification, GAD2 is a 15 amino acid sequence corresponding to residues 206-220 of GAD65 and is represented as SEQ. ID NO 4. All additional pending claims depend from claim 1. The claims do **not** specify that the protein fragment or peptide is full length GAD65 as asserted. The instant obviousness rejection was made based on a factually incorrect reading of the claim language. Withdrawal of this rejection is respectfully requested.

B. Essential elements missing from *prima facie* case.

The OA states that "...claim 26 reciting a fragment consisting of specific residues of GAD 65 is not included in the rejection because there is no teaching of employing a specific 14 (sic) amino acid fragment such as GAD2 represented by SEQ. ID NO 4. All other claims, however, encompass the use of full length GAD65 which is obvious." OA dated 10/08/2008 at page 7, 2nd paragraph. As pointed out above, **all** of the pending claims in fact specify that the "protein fragment or peptide is GAD2 represented by SEQ. ID NO 4," not the full length GAD65 protein. As such, no *prima facie* case has been established with respect to any claims just as the Office stated it had not been established with respect to claim 26. The OA response dated 08/07/2008 at pages 15 – 19 further sets forth the absence of essential elements needed for a *prima facie* case of obviousness of the presently pending claims when properly construed.

III. Rejection Under 35 U.S.C. 112, first paragraph.

Claims 1-5, 7, 13, 15-19 and 22-30 stand rejected under 35 U.S.C. 112, first paragraph as allegedly introducing new matter. This rejection contains clear factual error. The OA states that "[t]he specification does not teach the peptides as part of an immunoglobulin construct." This is clearly factually incorrect. GAD2 represented by SEQ. ID No. 4 is the only peptide presently claimed. Applicant draws the PTO's attention to page 45, line 20 – page 46, line 2 and reproduces that text for convenience:

> Other peptides that may be inserted within the variable region **within the CDR region of an Ig and utilized for creating compositions for the treatment of type 1 diabetes as taught in the present invention** are: GAD1 (Glutamic acid decarboxylase-65 also known as "GAD65"); corresponding to amino acid residues 524-543 of GAD 65 (Seq. I.D. No. 3 [SRLSKVAPVIKARMMEYGTT]) to create chimera Ig-GAD1; and 2) **GAD2; corresponding to amino acid residues 206-220 of GAD 65 (Seq. I.D. No. 4 [TYEIAPVFVLLEYVT])**; and other peptides derived from GAD65.

Clearly the specification teaches GAD2 as part of an immunoglobulin construct for use in the instant invention. Withdrawal of this rejection is therefore respectfully requested.

Conclusion

The application is believed to be in condition for allowance. Early and favorable considerations is respectfully requested.

Respectfully submitted,

BELL, BOYD & LLOYD LLP

BY _____
David B. Fournier
Reg. No. 51,696
October 30, 2008